SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alendronic Acid 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg alendronic acid (as alendronate sodium)

Excipients: Each tablet contains 38.867 mg of Lactose Anhydrous

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White to off-white, oval, biconvex tablet, debossed with '10' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures.
- Treatment of osteoporosis in men at increased risk of fracture. A reduction in the incidence of vertebral, but not of non-vertebral fractures has been demonstrated.
- Prophylaxis of glucocorticoid-induced osteoporosis.

Risk factors often associated with the development of osteoporosis include thin body build, family history of osteoporosis, early menopause, moderately low bone mass and long-term glucocorticoid therapy, especially with high doses (15 mg/day).

4.2 Posology and method of administration

Posology

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Alendronic Acid 10 mg Tablets on an individual patient basis, particularly after 5 or more years of use.

Treatment of post-menopausal osteoporosis:
The recommended dosage is 10 mg once daily.

Treatment of osteoporosis in men:
The recommended dosage is 10 mg once daily.

Treatment and Prevention of glucocorticoid-induced osteoporosis:
For post-menopausal women who are not receiving oestrogen treatment the recommended dose is one 10 mg tablet daily. For other populations, see summary of product characteristics for preparations that contain 5 mg alendronate

Elderly
In clinical trials there was no age-related difference with regard to efficacy or safety profiles of alendronate. Therefore no adjustment of the dose is necessary for elderly patients.

Renal impairment
No dose adjustment is necessary in patients with a glomerular filtration rate (GFR) greater than 35 ml/min. Alendronate is not recommended for patients with impaired renal function if the GFR is less than 35 ml/min, as there is no experience of this.

Use in impaired hepatic function No dose adjustment is necessary.

Paediatric population
Alendronate Sodium is not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis (See also section 5.1).

Method of administration

Oral use.

To obtain satisfactory absorption of alendronate Alendronic acid tablets must be taken on an empty stomach immediately on rising in the morning, with plain water only, at least 30 minutes before the first food, drink or other medication of the day. Other drinks (including mineral water), food and some medicines are likely to reduce the absorption of alendronate (see section 4.5).

To assist delivery to the stomach and thus reduce the risk of irritation/side effects locally and in the oesophagus (see section 4.4)
• Alendronic acid tablets should only be swallowed on rising for the day with a whole glass of water (not less than 200 ml).
• Alendronic acid tablets should be swallowed whole. The tablets should not be chewed, sucked or allowed to dissolve in the mouth on account of the risk of oropharyngeal ulceration.
• Patients should not lie down until after the first meal of the day, which must be at least 30 minutes after taking the tablet.
• Patients should not lie down within 30 minutes of taking Alendronic acid tablets
• Alendronic acid tablets should not be taken at bedtime or before arising for the day.

Patients should be given a calcium and vitamin D supplement if the diet is inadequate (see section 4.4).

4.3 Contraindications

Alendronic acid Tablet is contraindicated in:

• Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
• Inability to stand or sit upright for at least 30 minutes.
• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Hypocalcaemia.

4.4 Special warnings and precautions for use

Upper gastrointestinal adverse reactions

Alendronic acid can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronic acid is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, or ulcers or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty (see section 4.3). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture or perforation, have been reported in patients receiving alendronic acid. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronic acid and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronic acid tablet properly and/or who continue to take alendronic acid tablet after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient (see section 4.2). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

While no increased risk was observed in extensive clinical trials, there have been rare (post-

marketing) reports of gastric and duodenal ulcers, some severe and with complications.

Osteonecrosis of the jaw

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw:

- potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose
- cancer, chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors, smoking
- a history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with poor dental status.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

During bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Musculoskeletal pain
Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate

therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Skin reactions

In post-marketing experience, there have been rare reports of severe skin reactions including

Stevens Johnson syndrome and toxic epidermal necrolysis.

Renal impairment

Alendronic acid Tablet is not recommended for patients with renal impairment where GFR is

less than 35 ml/min, (see section 4.2).

Bone and mineral metabolism

Causes of osteoporosis other than oestrogen deficiency, ageing and glucocorticoid use should

be considered.

Hypocalcaemia must be corrected before initiating therapy with alendronic acid (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with alendronic acid.

Due to the positive effects of alendronic acid in increasing bone mineral, decreases in serum calcium and phosphate may occur, especially in patients taking glucocorticoids, in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare reports of symptomatic hypocalcaemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).
Ensuring adequate calcium and vitamin D intake is particularly important in patients receiving glucocorticoids.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronic acid. Therefore, patients must wait at least 30 minutes after taking alendronic acid tablet before taking any other oral medicinal product (see sections 4.2 and 5.2).

No other drug interactions of clinical significance are anticipated. Concomitant use of HRT (oestrogen ± progestin) and alendronic acid tablet was assessed in two clinical studies of one or two years duration in post-menopausal osteoporotic women (5.1 'Pharmacodynamic properties, *concomitant use with oestrogen/hormone replacement therapy (HRT)*').. Combined use of alendronic acid and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments.

Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

Although specific interaction studies were not performed, in clinical studies alendronic acid was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of alendronic acid in pregnant women. Studies in animals have shown reproductive toxicity. Alendronic acid given during pregnancy in rats caused dystocia related to hypocalcemia (see section 5.3).

‘Alendronic acid’ should not be used during pregnancy.

Breast-feeding

It is not known whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Alendronate not be used during breast-feeding.

Fertility
Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use (see section 5.2). There are no data on foetal risk in humans. However, there is a theoretical risk of foetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

4.7 Effects on ability to drive and use machines

‘Alendronic acid’ has no or negligible direct influence on the ability to drive and use machines. However, certain adverse reactions that have been reported with 'alendronic acid' may affect some patients' ability to drive or operate machinery. Individual responses to 'alendronic acid' may vary (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
‘Alendronic Acid ' has been studied in nine major clinical studies (n=5,886). In the longest running trials in post-menopausal women up to five years experience has been collected. Two years safety data are available in both men with osteoporosis and men and women on glucocorticoids.

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of ‘Alendronic acid’ Once weekly 70 mg (n=519) and alendronate 10mg/day (n=370) were similar.

In two three-year studies of virtually identical design, in post-menopausal women (alendronate 10mg: n=196, placebo: n-397) the overall safety profiles of alendronate 10mg/day and placebo were similar.

Adverse experiences reported by the investigators as possibly, probably or definitely drug-related are presented below if they occurred in ≥1% in either treatment group in the one-year study, or in ≥1% of patients treated with alendronate 10 mg/day and at a greater incidence than in patients given placebo in the three-year studies:

	One-Year Study		Three-Year Studies	
	'Alendronic acid' Once Weekly 70 mg (n = 519) %	alendronate 10 mg/day (n = 370) %	alendronate 10 mg/day (n = 196) %	Placebo (n = 397) %
Gastro-intestinal				
abdominal pain	3.7	3.0	6.6	4.8
dyspepsia	2.7	2.2	3.6	3.5
acid regurgitation	1.9	2.4	2.0	4.3

nausea	1.9	2.4	3.6	4.0
abdominal distention	1.0	1.4	1.0	0.8
constipation	0.8	1.6	3.1	1.8
diarrhoea	0.6	0.5	3.1	1.8
dysphagia	0.4	0.5	1.0	0.0
flatulence	0.4	1.6	2.6	0.5
gastritis	0.2	1.1	0.5	1.3
gastric ulcer	0.0	1.1	0.0	0.0
oesophageal ulcer	0.0	0.0	1.5	0.0
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	2.9	3.2	4.1	2.5
muscle cramp	0.2	1.1	0.0	1.0
Neurological				
headache	0.4	0.3	2.6	1.5

Tabulated list of adverse reactions

The following adverse experiences have been reported during clinical studies and/or post-marketing use:

Frequencies are defined as: Very common (≥1/10), Common (≥1/100, < 1/10), Uncommon (≥1/1,000, < 1/100), Rare (≥1/10,000, < 1/1,000), Very rare (< 1/10,000 including isolated cases)

System Organ Class	Frequency	Adverse Experience Term
Immune system disorders:	Rare	hypersensitivity reactions including urticaria and angioedema
Metabolism and nutrition disorders:	Rare	symptomatic hypocalcaemia, often in association with predisposing conditions[§.]
Nervous system disorders:	Common	headache, dizziness[†]
	Uncommon	dysgeusia[†]
Eye disorders:	Uncommon	eye inflammation (uveitis, scleritis, episcleritis)
Ear and labyrinth disorders:	Common	Vertigo[†]
	Very rare	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Gastro-intestinal disorders:	Common:	abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation
	Uncommon:	nausea, vomiting, gastritis, oesophagitis*,oesophageal erosions*, melena[†]

	Rare:	oesophageal stricture*, oropharyngeal ulceration*, upper gastro-intestinal PUBs (perforation, ulcers, bleeding)[§]
Skin and subcutaneous tissue disorders:	Common:	alopecia[†], pruritus[†]
	Uncommon:	rash, erythema
	Rare:	rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis[‡]
Musculoskeletal and connective tissue disorders:	Very common:	musculoskeletal (bone, muscle or joint) pain which is sometimes severe[†§]
	Common:	joint swelling[†]
	Rare:	Osteonecrosis of the jaw[‡§]; atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)[⊥]
General disorders and administration site conditions:	Common:	asthenia[†], peripheral oedema[†]
	Uncommon:	transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment[†].

[§]*See section 4.4*

†Frequency in Clinical Trials was similar in the drug and placebo group.

**See sections 4.2 and 4.4*

‡This adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials.

[⊥]*Identified in postmarketing experience.*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.

Management

No specific information is available on the treatment of overdosage with Alendronic acid. Milk or antacids should be given to bind alendronic acid. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs affecting bone structure and mineralisation, bisphosphonates.

ATC code: M05BA04

Mechanism of action

Alendronic acid is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. The bone formed during treatment with alendronic acid is of normal quality.

Clinical efficacy and safety

Treatment of post-menopausal osteoporosis

The effects of alendronic acid on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

In the initial efficacy studies, the mean bone mineral density (BMD) increases with alendronic acid 10 mg/day relative to placebo at three years were 8.8%, 5.9% and 7.8% at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48% reduction in the proportion of patients treated with alendronic acid experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies BMD at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.

FIT consisted of two placebo-controlled studies: a three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture and a four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture, 37% of whom had osteoporosis as defined by a baseline femoral neck BMD at least 2.5 standard deviations below the mean for young, adult women. In all FIT patients with osteoporosis from both studies, alendronic acid reduced the incidence of: ≥ 1 vertebral fracture by 48%, multiple vertebral fractures by 87%, ≥1 painful vertebral fracture by 45%, any painful fracture by 31% and hip fracture by 54%.

Overall these results demonstrate the consistent effect of alendronic acid to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with the greatest morbidity.

Prevention of post-menopausal osteoporosis

The effects of ‘Alendronic acid’ to prevent bone loss were examined in two studies of post-menopausal women aged ≤60 years. In the larger study of 1,609 women (≥6 months post-menopausal) those receiving ‘Alendronic acid’ 5mg daily for two years had BMD increases of 3.5%, 1.3%, 3.0% and 0.7% at the spine, femoral neck, trochanter and total body, respectively. In the smaller study (n=447), similar results were observed in women (6 to 36 months post-menopausal) treated with ‘Alendronic acid’ 5mg daily for three years. In contrast, in both studies, women receiving placebo lost bone mass at a rate of approximately 1% per year. The longer term effects of ‘Alendronic acid’ in an osteoporosis prevention population are not known but clinical trail extensions of up to 10 years of continuous treatment are currently in progress.

Concomitant use with oestrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with alendronic acid tablet 10 mg once-daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year study of hysterectomised, post-menopausal, osteoporotic women. At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or alendronic acid tablet alone (both 6.0%).

The effects on BMD when alendronic acid tablet was added to stable doses (for at least one year) of HRT (oestrogen ± progestin) were assessed in a one-year study in post-menopausal, osteoporotic women. The addition of alendronic acid tablet 10 mg once-daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favourable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck and trochanter. No significant effect was seen for total body BMD.

Treatment of osteoporosis in men

The efficacy of alendronic acid tablet 10 mg once daily in men (ages 31 to 87; mean, 63) with osteoporosis was demonstrated in a two-year study. At two years, the mean increases relative to placebo in BMD in men receiving alendronic acid tablet 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Alendronic acid tablet was effective regardless of age, race, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with much larger studies in post-menopausal women, in these 127 men, alendronic acid tablet 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%) and, correspondingly, also reduced height loss (-0.6 vs. -2.4 mm).

Glucocorticoid-induced osteoporosis

The efficacy of alendronic acid tablet 5 and 10 mg once daily in men and women receiving at least 7.5 mg/day of prednisone (or equivalent) was demonstrated in two studies. At two years of treatment, spine BMD increased by 3.7% and 5.0% (relative to placebo) with alendronic acid tablet 5 and 10 mg/day respectively. Significant increases in BMD were also observed at the femoral neck, trochanter, and total body. In post-menopausal women not receiving oestrogen, greater increases in lumbar spine and trochanter BMD were seen in those receiving 10 mg alendronic acid tablet than those receiving 5 mg. Alendronic acid tablet was effective regardless of dose or duration of glucocorticoid use. Data pooled from three dosage groups (5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) showed a significant reduction in the incidence of patients with a new vertebral fracture at two years (Alendronic acid 0.7% vs. placebo 6.8%).

<u>Laboratory test findings</u>
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking 'Alendronic acid' versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

<u>Paediatric population</u>

Alendronate sodium has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta.

5.2 Pharmacokinetic properties

Absorption

Relative to an intravenous reference dose, the oral mean bioavailability of alendronic acid tablet in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability was decreased similarly to an estimated 0.46% and 0.39% when alendronic acid tablet was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronic acid tablet was effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible whether alendronic acid was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronic acid tablet with coffee or orange juice reduced bioavailability by approximately 60%.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronic acid tablet (a mean increase ranging from 20% to 44%).

Distribution

Studies in rats show that alendronic acid tablet transiently distributes to soft tissues following 1 mg/kg intravenous administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of drug in plasma following therapeutic oral doses are too low for analytical detection (<5 ng/ml). Protein binding in human plasma is approximately 78%.

Biotransformation

There is no evidence that alendronic acid is metabolised in animals or humans.

Elimination

Following a single intravenous dose of [^{14}C] alendronic acid tablet, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg intravenous dose, the renal clearance of alendronic acid tablet was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within six hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronic acid from the skeleton. Alendronic acid tablet is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

Renal impairment

Preclinical studies show that the drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronic acid via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronic acid in bone might be expected in patients with impaired renal function (see section 4.2).

5.3 Preclinical safety data

In test animal species the main target organs for toxicity were kidneys and gastro-intestinal tract. Renal toxicity was seen only at doses >2 mg/kg/day orally (ten times the recommended dose) and was evident only on histological examination as small widely scattered foci of nephritis, with no evidence of effect on renal function. The gastro-intestinal toxicity, seen in rodents only, occurred at doses >2.5 mg/kg/day and appears to be due to a direct effect on the mucosa. There is no additional relevant information.

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3,256 mg/m^2) and 966 mg/kg (2,898 mg/m^2) (equivalent to human oral doses* of 27,600 and 48,300 mg), respectively. In males, these values were slightly higher, 626 and 1,280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4,000 mg/m^2) (equivalent to a human oral dose* of 10,000 mg).

* Based on a patient weight of 50 kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Cellulose microcrystalline (E460)
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Opaque white PVC/ALU blister
Pack size: 14 tablets , 28 tablets, , 30 tablets , 50 tablets , 56 tablets , 84 tablets , 90 tablets, 98 tablets, 112* tablets or 140* tablets.
Not all pack sizes may be marketed.

* Not for UK market

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited

Sage House

319, Pinner Road

North Harrow

Middlesex HA1 4 HF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0070

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/09/2008

10 DATE OF REVISION OF THE TEXT

17/11/2021